REMARKS

Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are defined as thrombotic microangiopathies. Contributing factors to the pathophysiology of TTP and HUS are believed to be endothelial cell damage and primary platelet aggregation. Also, patients with TTP and HUS have elevated levels of plasminogen activator inhibitor (PAI-1) and decreased levels of protein C activity. Left untreated, TTP and HUS have a poor prognosis with mortality rates reaching 90%. Surviving patients often develop end-stage renal failure. Until now, the only treatment method for these disorders having a favorable outcome has been plasma exchange (PE) with fresh frozen plasma. Also, no FDA-approved treatment is currently available for TTP or HUS. Applicants discovered that human patients suffering from TTP or HUS could be treated with protein C, human protein C zymogen, or human activated protein C (hereafter protein C), thereby avoiding the complications and side effects associated with PE. Protein C, with its anticoagulant and profibrinolytic activities along with its ability to inactivate PAI-1, is useful for treatment of the occlusion of arterioles and capillaries by microthrombi that occur in patients with TTP or HUS.

Regarding the Examiner's inquiry about joint inventors and commonly owned claims, Applicants confirm that the subject matter of the claims was commonly owned at the time of invention.

Claims 1-20 are pending in this case.

REJECTION OF CLAIMS 1-5 and 6-20 UNDER 35 U.S.C. § 103(a)

Claims 1 through 5 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Glas-Greenwalt et al. (J. Lab Clin. Med., 1986, Vol. 108: 415-422), Gruber et

al. (Circulation, 1990, Vol. 82: 578-585), and Foster et al. (US 5,516,650 5/14/1996). Claims 6 through 20 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Glas-Greenwalt et al., Gruber et al., and Foster et al, and further in view of Hollenbeck et al. (Nephrol. Dial. Transplant., 1998, Vol. 13: 76-81). Applicants respectfully assert that the Examiner has failed to set forth a *prima facie* case of obviousness and request withdrawal of this rejection.

In *Graham v. John Deere Co.*, 383 U.S. 1 (1966), the court defined the test for determining obviousness under 35 U.S.C. § 103: 1) determine the scope and content of the prior art; 2) ascertain the differences between the prior art and the claims at issue; 3) resolve the level of ordinary skill in the pertinent art; and 4) evaluate evidence of secondary considerations. The USPTO bears the burden of establishing a *prima facie* case. (*In re Piasecki*, 745 F.2d 1468 (Fed. Cir. 1984)). In order to establish a *prima facie* case, the Examiner must show 1) some suggestion or motivation to modify the reference or to combine reference teachings (*In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988)); 2) the proposed modification had a reasonable expectation of success by a skilled artisan at the time of the invention (*Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200 (Fed. Cir. 1991)); and 3) the prior art reference or combination of references must teach or suggest all limitations of the claims (*In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991)). Applicants assert that the Examiner has not met the burden of establishing a *prima facie* case of obviousness.

Furthermore, Applicants respectfully submit that the combination of references cited by the Examiner is due to impermissible hindsight reasoning and not by a suggestion or motivation to modify or combine these references. According to *In re Geiger*, 815 F.2d 686 (Fed. Cir. 1987), the art must

contain some teaching with respect to combining the art in those references before combined so to avoid hindsight.

Applicants discovered an important, previously unknown method for treating patients suffering from thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) using protein C, human protein C zymogen, or human activated protein C (hereafter protein C). The Examiner points to separate elements from Glas-Greenwalt, Gruber, and Foster that allegedly were combined to make Claims 1 through 5 of the invention obvious. First of all, Glas-Greenwalt teaches that plasma exchange (PE) resulted in temporary reversal of abnormal levels for three factors (inhibitor of plasminogen activator (IPA), tissue plasminogen activator (t-PA), and protein C) in four of five patients with TTP. The Examiner views PE as a source for protein C replacement since "plasma contain[s] nascent or activated PC . . . [when] obtained from non-effected individuals." While protein C is present in plasma, PE is not a means for protein C supplementation. First, PE is used to remove antibodies or inhibitors from a patient's blood and not to provide protein C. Thus, PE is a means for removal not replacement. Second, PE did not affect protein C levels alone. Both IPA and t-PA levels changed along with protein C levels upon PE. Even if PE was a means for replacement, Glas-Greenwalt's results do not direct the reader to adjust protein C in isolation in order to affect TTP. Third, plasma has many components beyond just protein C, IPA, and t-PA. Plasma also contains various components such as water, proteins (e.g. albumin, gammaglobulins, fibrinogens, etc.), organic nutrients (carbohydrates, amino acids, lipids, vitamins, etc.), hormones, electrolytes, and cellular wastes (carbon dioxide, urea, etc.). Since numerous plasma components become available to a patient treated with PE, isolating PE as a source of protein C - and not any other plasma component -

that then affects TTP is a conclusion made in hindsight. Furthermore, Glas-Greenwalt specifically states that "[w]hether repeated, although temporary, reversal of fibrinolytic and protein C abnormalities by plasma exchange contributes to the beneficial effects of this treatment . . . remain speculative." Thus, even the authors are uncertain as to the role of plasma exchange and protein C on treatment of TTP. At no time does Glas-Greenwalt suggest modifications or combinations with other references that would lead to the invention nor does it motivate the skilled artisan to utilize this reference to arrive at using protein C to treat TTP in human patients. Furthermore, the skilled artisan would not have a reasonable expectation of success when using protein C to treat TTP since PE 1) is not a means for replacement (for protein C or any other particular component), 2) affected the levels of IPA, t-PA, and protein C, 3) and at best resulted in temporary reversal of TTP-related abnormalities.

Second, Gruber involves the use of recombinant activated protein C (rAPC) to inhibit thrombus formation in baboons, not human patients. The Examiner states that this nonhuman primate study would motivate the skilled artisan to extend the use of rAPC to humans with the appropriate dosage and infusion methods. While rAPC has anticoagulant and profibrinolytic properties, the use of rAPC in humans is not obvious from the results shown in baboons. Of particular importance is the fact that the dosages taught in Gruber do not extend to human treatment. In fact, the high dosages (0.25 and 1.0 mg/kg-hr) that provide promising results in baboons are highly likely to result in serious adverse events in humans. Plus, the main etiology for TTP is complications due to severe infection, an understanding that is unavailable from the purely thrombotic baboon model. Also, this baboon model is limited to teaching about thrombus prevention and does not teach about the reversal of organ dysfunction or

reduced mortality for humans. These points particularly refute the Examiner's assertion that Gruber's work in baboons would suggest to the skilled artisan use of rAPC for humans. Furthermore, Gruber would in no way motivate the skilled artisan to extend the use of rAPC to treat TTP since TTP is not part of this reference.

Third, the Examiner reaches to Foster to provide motivation for the development and use of recombinant activated protein C over plasma derived protein C. Foster teaches methods for producing a protein which has substantially the same biological activity as human protein C or human activated protein C, having modifications that enhance the cleavage of the proteins between the light and heavy chains. While the Examiner states that the skilled artisan would be motivated to develop and use recombinant protein C "to avoid contamination of the final protein C product with potential bacterial or viral pathogens," Foster's methods are directed to modified human protein C and human activated protein C. Even if Foster taught methods for unmodified human protein C and human activated protein C, there is no suggestion or motivation to modify this reference or to combine reference teachings so to treat TTP. In fact, TTP is never mentioned in Foster. Ultimately, Foster's teachings are in no way linked to Applicants' invention involving a method of treating a patient suffering from TTP with protein C.

The Examiner also alleges that Claims 6 through 20 are obvious due to Glas-Greenwalt, Gruber, and Foster and further in view of Hollenbeck. Glas-Greenwalt, Gruber, and Foster do not teach methods for using protein C to treat HUS. Yet, Hollenbeck does state that TTP and HUS are considered as one entity because of similarities in clinical and morphological findings. Thus, the Examiner utilizes Hollenbeck to link HUS with TTP and thereby bridge the gap

between Hollenbeck with the previously noted art that lacks HUS application. Actually, TTP and HUS are similar disorders, with TTP usually affecting adults and HUS usually affecting children. According to Hollenbeck, the causes for HUS-TTP syndrome (Hollenbeck's terminology) differ for children and adults. Nevertheless, the arguments against obviousness presented for Glas-Greenwalt, Gruber, and Foster with respect to TTP equally apply for HUS.

Hollenbeck teaches that plasma exchange with fresh-frozen plasma (PE) "is the only treatment modality for which a favourable influence on the course of the disease has been shown in prospective studies. . . . we recommend early and intensive PE in patients with HUS-TTP." Again, as with Glas-Greenwalt, the Examiner states that "[i]t is also well known in the art that plasma is [a] source of protein C and activated protein C." As previously noted, protein C is present in plasma; however, PE is not a means for protein C supplementation. PE is instead a means for removal not replacement, not utilized to replace protein C but to remove antibodies or inhibitors from a patient's blood. Plus, plasma contains many components such as water, proteins, organic nutrients, hormones, electrolytes, and cellular wastes. PE treatment makes numerous plasma components available to a patient. However, isolating PE as a protein C source that affects TTP while excluding all other plasma components is a conclusion made in hindsight. More particularly, at no time does Hollenbeck teach anything whatsoever with regard to protein C usage. Thus, since protein C is never mentioned and PE is not considered a protein C supplementation source, this reference does nothing to motivate the skilled artisan to utilize its teachings to arrive at using protein C to treat TTP and HUS in human patients. Also, Hollenbeck points to PE as the only favorable treatment for HUS-TTP, thereby providing no teachings that would lead to Applicants' invention.

Additionally, "the Examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor. . . would select the elements from the cited prior art references for combination in the manner claimed." (*In re Rouffet*, 149 F.3d 1350 (Fed. Cir. 1998)). The cited references do not disclose nor even suggest using protein C for treatment of TTP and HUS in humans. In fact, these references are directed to four separate concepts, none of which add up to the invention even if a suggestion to modify or combine had been asserted. Glas-Greenwalt teaches that PE affected the levels of t-PA, IPA, and protein C in patients with TTP and at best resulted in temporary reversal of TTP-related abnormalities. Gruber teaches that rAPC inhibits thrombus formation in baboons, not humans. The baboon model in Gruber does not extend to humans because 1) the high dosages successfully used for baboons are highly likely to result in serious adverse events in humans, 2) the main etiology for TTP in humans cannot be derived from the baboon model, and 3) the baboon model provides no understanding of organ dysfunction reversal or reduced mortality for humans. Foster teaches how to make modified protein C and activated protein C and has no connection to TTP treatment. Hollenbeck links TTP and HUS and states that the only favorable treatment for HUS-TTP is PE. Also, Hollenbeck has no reference to protein C. Thus, it follows that the skilled artisan would not be motivated by the cited references to treat human patients suffering from TTP or HUS using protein C.

TTP and HUS are defined as thrombotic microangiopathies characterized by occlusion of arterioles and capillaries by microthrombi, thrombocytopenia, impairment of neurologic function, and progressive renal failure. Applicants' invention is directed to the treatment of a patient suffering from TTP or HUS with protein C, human protein C zymogen, or human activated protein C (previously

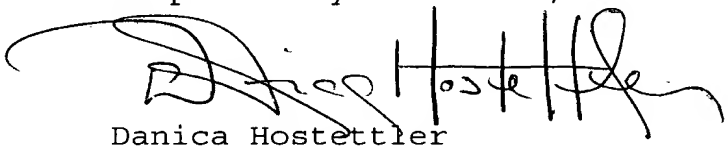
noted as protein C). The invention further claims a particularized dose and plasma level as well as the means of administration via continuous infusion and/or bolus injection. No evidence exists of any suggestion or motivation to modify or combine teachings from the cited prior art references. Only through the benefit of impermissible hindsight can one selectively navigate through the cited references to arrive at the invention. For the above-stated reasons, Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

Applicants assert that the above-stated remarks obviate the noted rejections. This invention is not obvious since there is no suggestion or motivation to modify or combine teachings from Glas-Greenwalt, Gruber, Foster, or Hollenbeck. Also, there is no reasonable expectation of success based on modifications of these references. Only impermissible hindsight could provide an allegedly obvious path by which one could make the invention.

In view of these points, Applicants courteously solicit reconsideration of these rejections and passage of this case to issuance.

Respectfully submitted,



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